Role of the glycocalyx in pre-eclampsia

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The principal aim of this study is to elucidate the role of the glycocalyx in the pathogenesis of pre-eclampsia by assessing: - Whether the glycocalyx is affected in pre-eclampsia and is related to its severity.- Whether glycocalyx perturbation is...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Maternal complications of pregnancy
Study type	Observational invasive

Summary

ID

NL-OMON36757

Source
ToetsingOnline

Brief title
Glycocalyx and pre-eclampsia

Condition

- Maternal complications of pregnancy

Synonym
hypertension in pregnancy, toxemia of pregnancy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw- klinische fellowship

Intervention

Keyword: anti-angiogenic factors, cerebral autoregulation, glycocalyx, pre-eclampsia

Outcome measures

Primary outcome

Differences in glycocalyx volume between patients with pre-eclampsia and healthy pregnant controls as indirectly estimated by SDF imaging and measurement of glycocalyx constituents and enzymes in plasma at admission to the hospital and 3 months after delivery of the baby.

Secondary outcome

- Association between severity of pre-eclampsia and glyocalyx perturbation as assessed by SDF imaging, levels of glycocalyx constituents and enzyme activity.

- Association between glycocalyx perturbation in patients with pre-eclampsia and coagulation abnormalities.

- Association between glycocalyx perturbation and levels of anti-angiogenic factors (sFLT-1 and sEndoglin) in patients with pre-eclampsia.

Study description

Background summary

Pre-eclampsia is a potentially life threatening disorder affecting 2-7% of pregnant nulliparous women and is a leading cause of maternal and neonatal morbidity and mortality in the Netherlands. Hallmarks of pre-eclampsia are a systemic increase in vascular permeability and vasomotor tone, proteinuria and a prothrombotic state. Maternal death is in most cases attributable to cerebrovascular complications, believed to result from impaired cerebral autoregulation and increased permeability of the blood-brain barrier. Even after delivery, patients with a history of pre-eclampsia remain at increased risk for future cardiovascular complications and have a disturbed flow mediated vasodilatation.
The glycocalyx is a layer of complex sugars lining the endothelium and a critical determinant of vascular homeostasis in humans. The glycocalyx

regulates vascular permeability for macromolecules particularly in the glomerulus and is involved in vessel tone regulation by mediating shear-dependent NO release.In addition, the glycocalyx has potent anti-thrombotic effects. Because of recent experiments and previous observations we believe that damage to the endothelial glycocalyx may play a pivotal role in pre-eclampsia.
First, artificial degradation of the glycocalyx in mice by hyaluronidase infusion, leads to a profound increase in proteinuria and systemic vascular leakage thereby resembling the findings of pre-eclampsia. Second, mRNA expression of various (placental) glycoproteins is up to 32 fold up-regulated in placental tissue from pre-eclamptic women compared to placental tissue from women with healthy pregnancy supporting a role for the glycocalyx in pre-eclampsia. Third, the glycocalyx is intimately involved in VEGF and TGF-beta signaling by mediating their binding to the endothelial cell surface receptor, FLT-1 and endoglin respectively. The soluble circulating form of these cell-surface receptors are associated with an increased risk of pre-eclampsia. Perturbation of the glycocalyx may very well result in the release of these receptors from the endothelial cell surface and thereby provide an alternative explanation for the association between these soluble antiangiogenic factors and the risk of pre-eclampsia.
Based on these observations we hypothesize that perturbation of the endothelial glycocalyx is important in the pathogenesis of pre-eclampsia and is associated with increased vascular permeability, vasomotor tone and coagulation.

Study objective

The principal aim of this study is to elucidate the role of the glycocalyx in the pathogenesis of pre-eclampsia by assessing:
- Whether the glycocalyx is affected in pre-eclampsia and is related to its severity.
- Whether glycocalyx perturbation is associated with increased permeability, vasomotor tone and coagulation in pre-eclampsia.
- Whether glycocalyx perturbation is associated with disturbances in cerebral autoregulation
- Whether glycocalyx perturbation is associatied with soluble FLT-1 and Endoglin, the circulating membrane receptors of VEGF and TGF-beta

Study design

A case-control design is chosen to compare patients with pre-eclampsia and healthy pregnant controls matched for maternal and gestational age. Patients with pre-eclampsia and healthy pregnant controls will be approached to participate in the study. They will be informed about the rationale of this study, possible risks and study burden. Eligible candidates who are willing to participate will be asked to provide informed consent. The study consists of

three visits: one screening visit, one visit for non-invasive measurements within 24 hrs after the screening visit and one visit 12 weeks after delivery. During the screening visit a brief history and physical examination will be performed. At the second and at the third visit a 24 hour urine sample will be collected and the following non-invasive measurements will be performed: 1. conventional sphygmomanometry will be used to measure BP, 2. glycocalyx dimensions will be visualized using SDF imaging, 3. noninvasive finger arterial pressure waveform registration by Nexfin (BMeye, Amsterdam, The Netherlands) will be used for continuous monitoring of heart rate, blood pressure, cardiac stroke volume, cardiac output, and peripheral vascular resistance, 4. transcranial Doppler (TCD) measurement will be performed to assess cerebral blood flow velocity of the medial cerebral artery. Finally, a blood sample will be drawn for standard laboratory assessments, measurement of coagulation, glycocalyx constituents and enzymes, and anti-angiogenic agents. A third visit will be planned 12 weeks after delivery of the baby. During this final visit the same procedures will be undertaken as in the second visit. In addition to these measurements flow mediated vasodilatation will be non-invasively assessed by foreman plethysmography.

Study burden and risks

Participants will be asked to spend approximately 2 hours spread over 3 visits to the measurements. At 2 visits a blood sample will be drawn via a venous puncture totalling 100 ml (50 ml at each visit). These wil be combined if possible with routine blood sample collection. There are no risks besides a mild sore spot or hematoma at the site of the venipuncture. All other measurements are non-invasive and are not harmful to mother and child.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Pre-eclampsia, defined as 1) hypertension (>140/90 mmHg) on at least two separate occasions and 2) proteinuria (>300 mg/24 hrs)
Pregnancy 20 weeks or more gestation
Age 18-42 years
Able to provide written informed consent

Exclusion criteria

Any chronic inflammatory condition
Primary renal disease
Diabetes mellitus or gravidarum
Smoking
Anti-phospholipid antibody syndrome
Eclampsia (e.g. convulsions, restlessness, somnolence, hyperreflexia)
Need for intravenous BP lowering therapy or magnesiumsulphate

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2011
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL33149.018.11